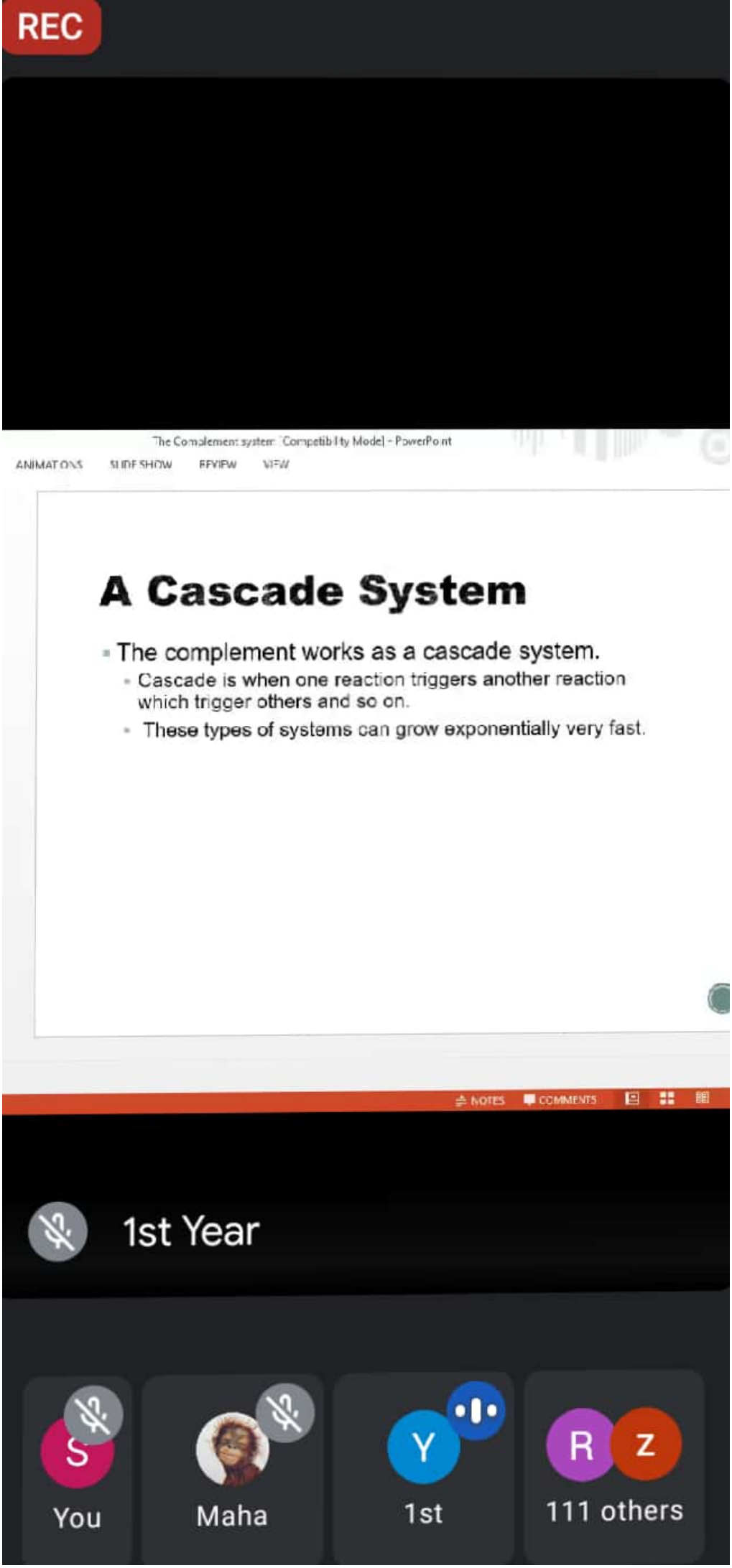
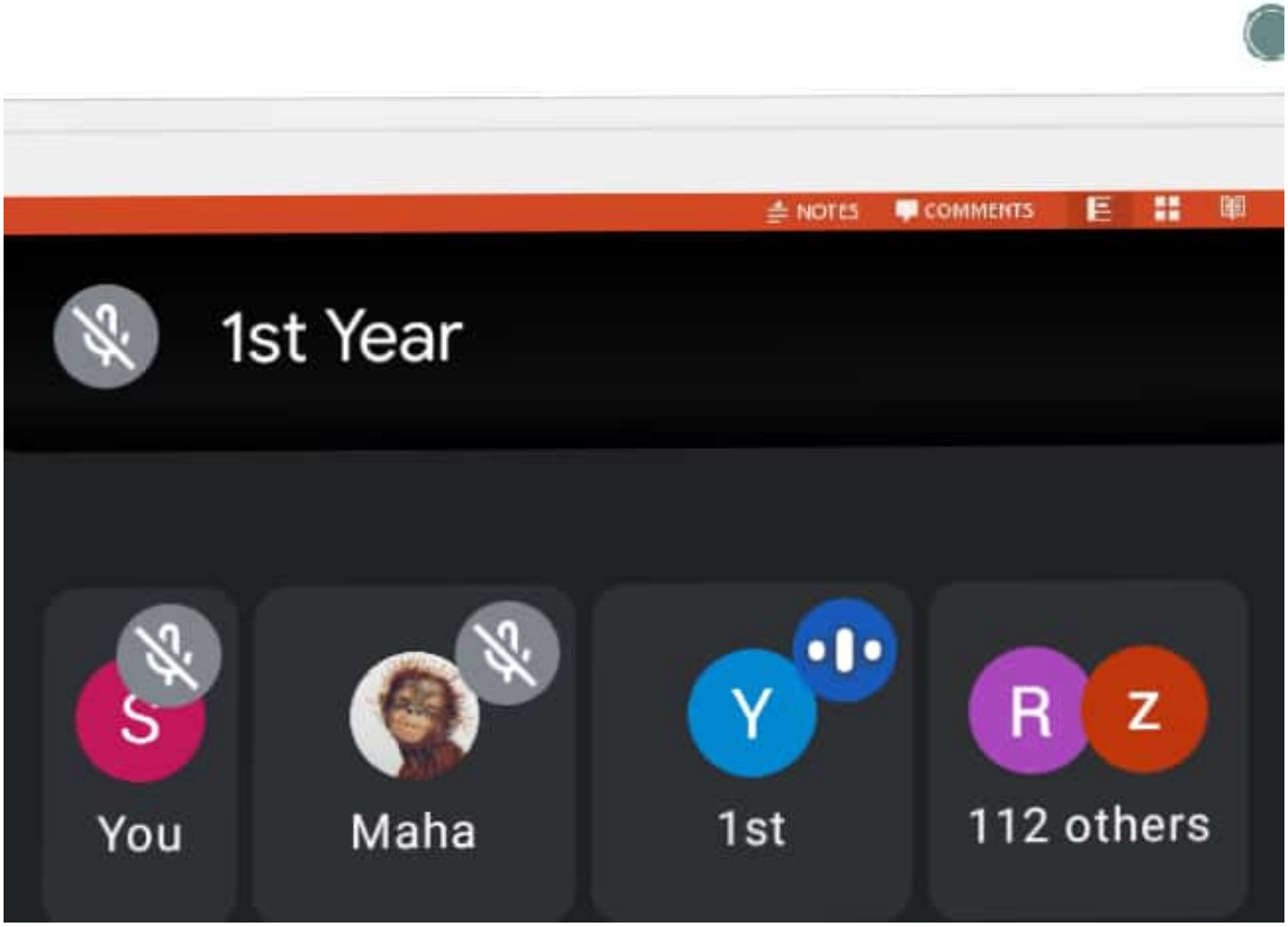
The complement system

- A defensive system consisting of over 30 proteins produced by the liver and found in circulating blood serum.
- The main proteins are 11 in number, C1- 9, B and D
- Complement kills microbes in three different ways
  - 1. Opsonization
  - 2. Inflammation
  - 3. Cytolysis



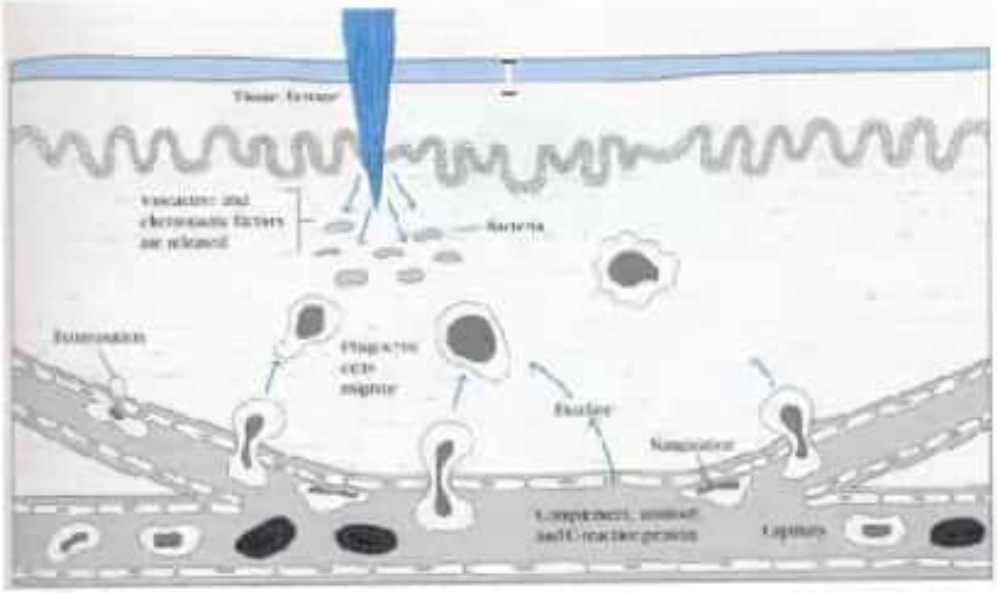
Cascade activation

- Complement proteins are often designated by an uppercase letter C and are inactive until they are split into products.
  - Example: C1
- When the products are split they become active. The active products are usually designated with a lower case a or b.
  - Example: C1a and C1b



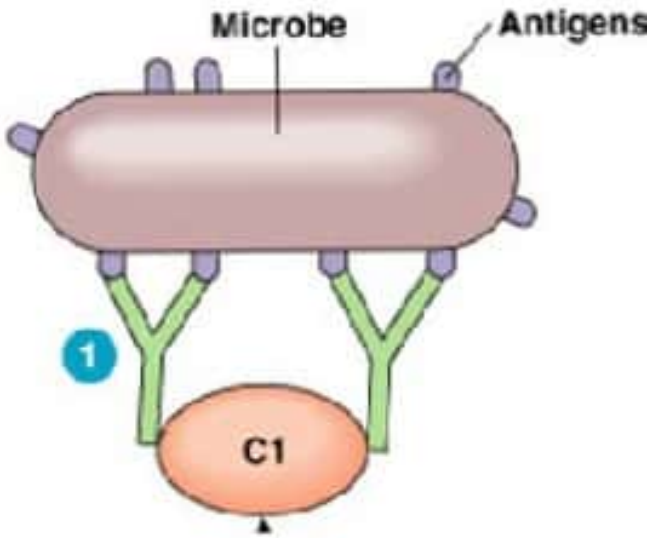
Two Pathways

- The complement pathway can be activated by either of two different pathways.
  - Classical pathway (specific immune system)
  - Alternative (non-specific immune system)



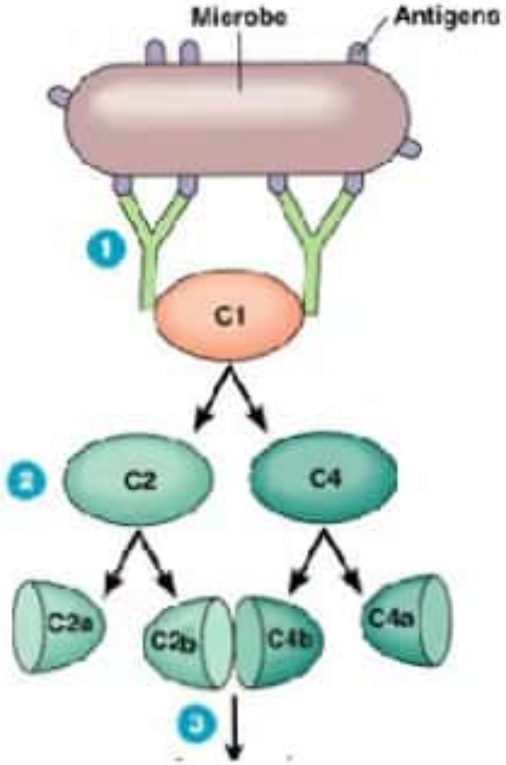
The Classical Pathway

- The classical pathway is considered to be part of the specific immune response because it relies on antibodies to initiate it.
- C1 becomes activated when it binds to the ends of antibodies



The building of a C3 activation complex

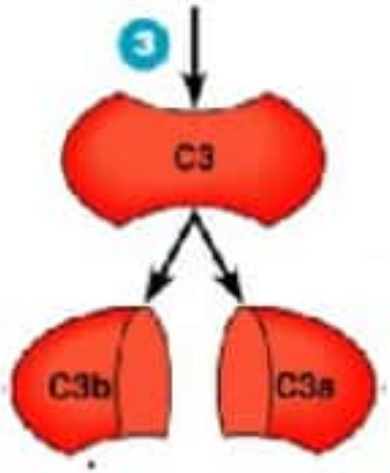
- Once C1 is activated, it activates 2 other complement proteins, C2 and C4 by cutting them in half
- C2 is cleaved into C2a and C2b
- C4 is cleaved into C4a and C4b
- Both C2b and C4b bind together on the surface of the bacteria
- C2a and C4a diffuse away



C3 Activation Complex (C3 Convertase)

- C2b and C4b bind together on the surface to form a C3 activation complex

- The function of the C3 activation complex is to activate C3 proteins.
  - This is done by cleaving C3 into C3a and C3b



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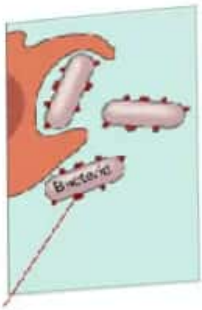
C3b

- Many C3b molecules are produced by the C3 activation complex.
- The C3b bind to and coat the surface of the bacteria.

- C3b is an opsonin
  - Opsonins are molecules that bind both to bacteria and phagocytes
  - Opsonization increases phagocytosis by 1,000 fold.



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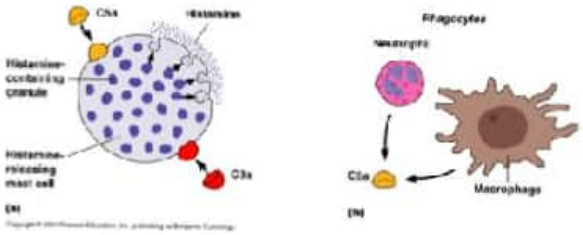
C3a



C3a increases the inflammatory response by binding to mast cells and causing them to release histamine

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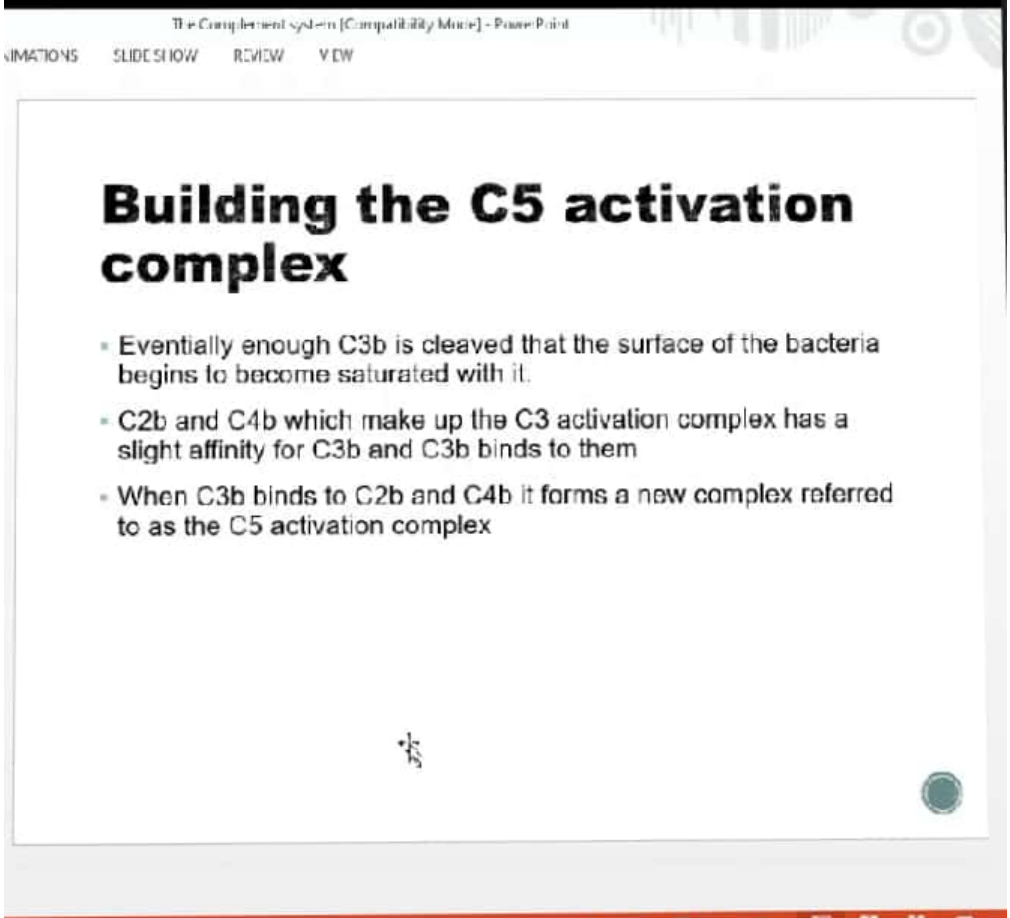
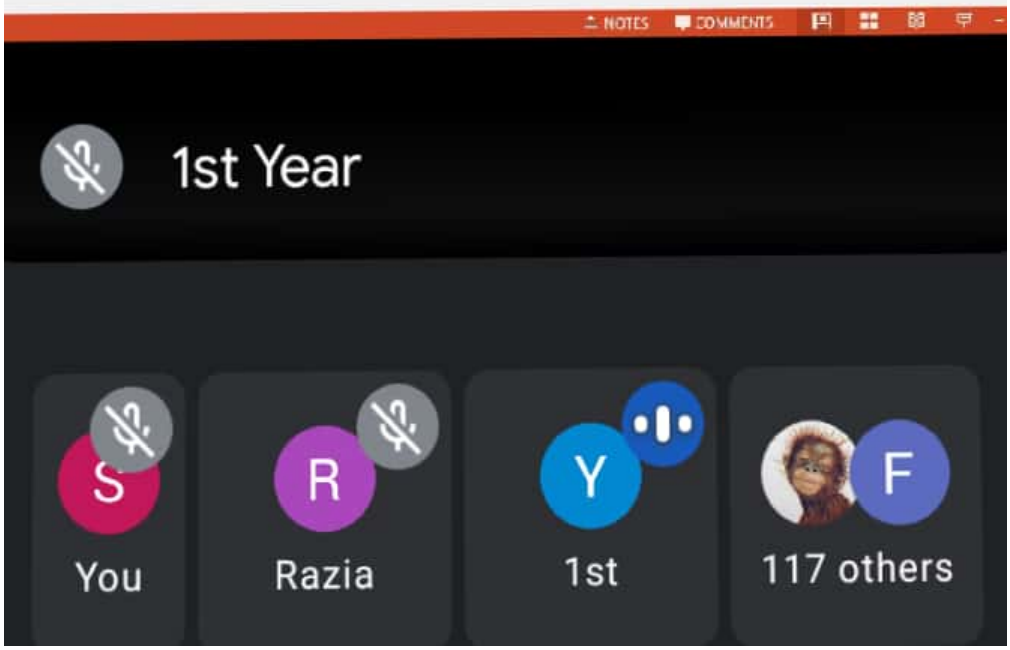
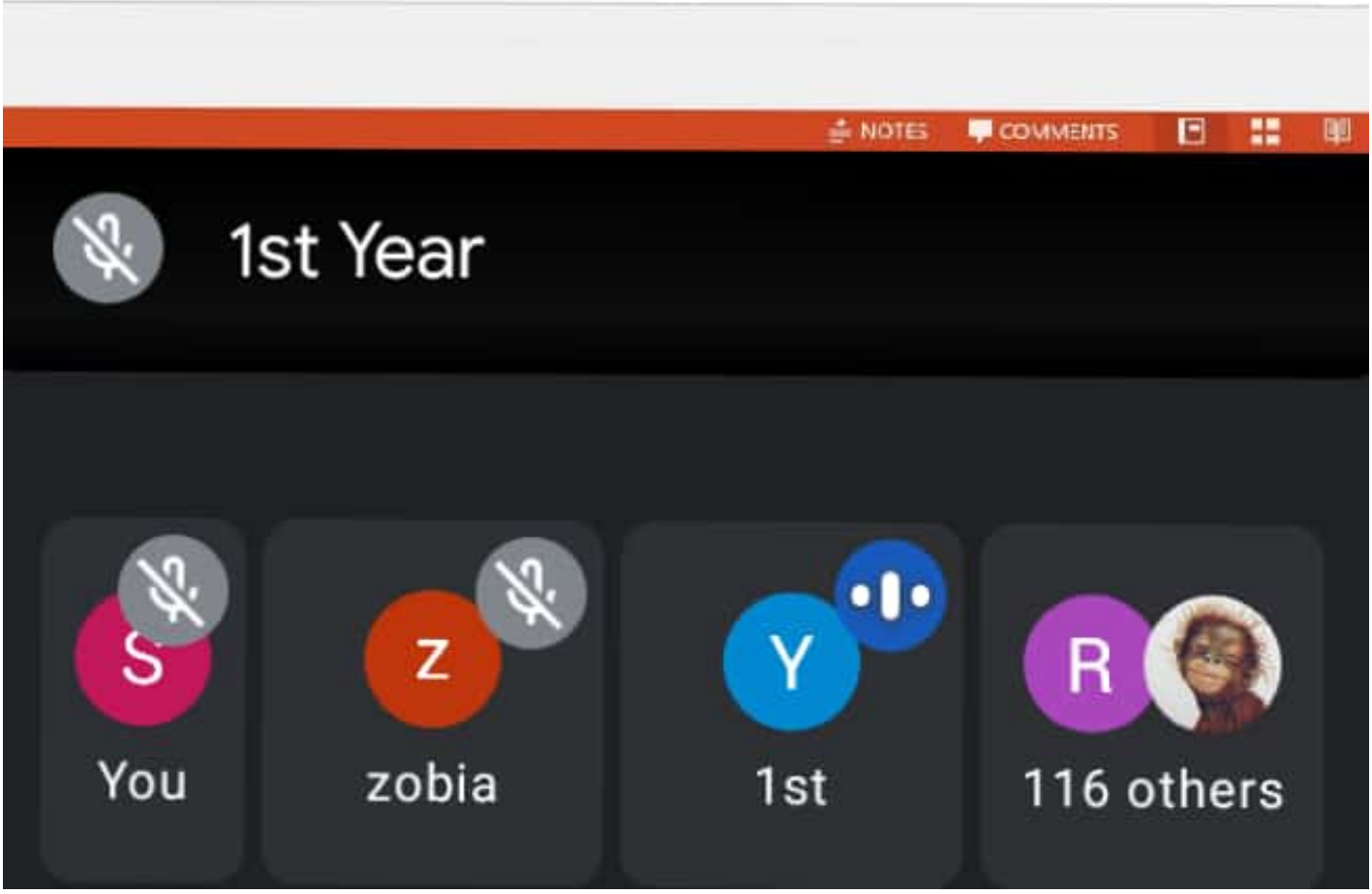


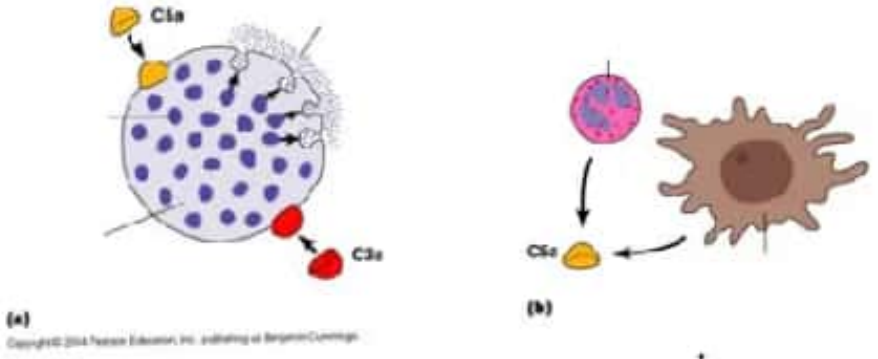


The C5 activation complex (C5 Convertase)

- The C5 activation complex (C2b, C4b, C3b) activates C5 proteins by cleaving them into C5a and C5b
- Many C5b proteins are produced by the C5 activation complex. These C5b begin to coat the surface of the bacteria.



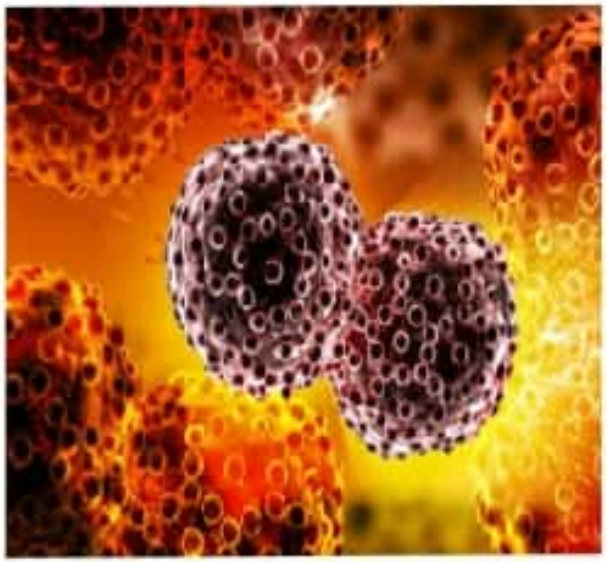
The function of C5a



- C5a disperses away from the bacteria.
  - Binds to mast cells and increases inflammation.
  - Most powerful chemotactic factor known for leukocytes

Building the Membrane Attack complex

- C5b on the surface of bacteria binds to C6
- The binding of C6 to C5b activates C6 so that it can bind to C7
- C7 binds to C8 which in turn binds to many C9's
- Together these proteins form a circular complex called the Membrane attack complex (MAC)



Building the Membrane Attack complex

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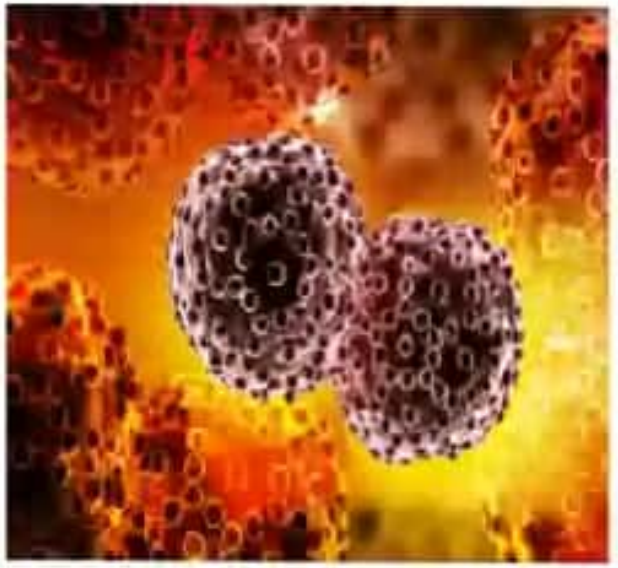
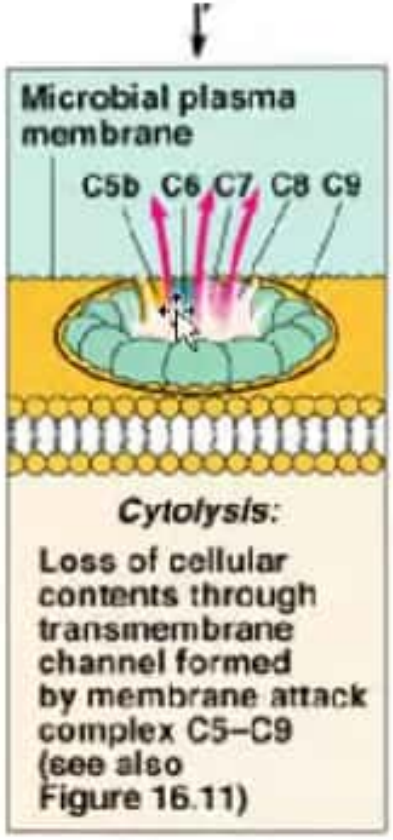


Membrane Attack complex

- The MAC causes Cytolysis.
  - The circular membrane attack complex acts as a channel in which cytoplasm can rush out of and water rushes in.
- The cells inner integrity is compromised and it dies



Membrane-Attack Complex

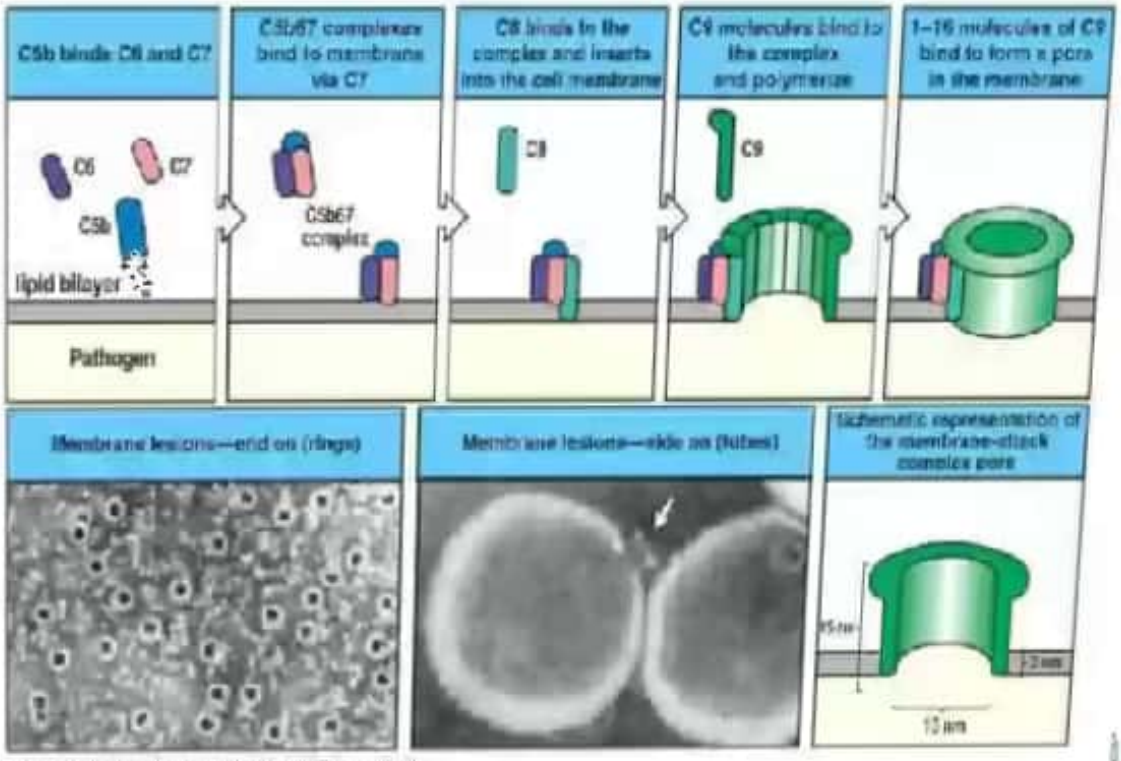
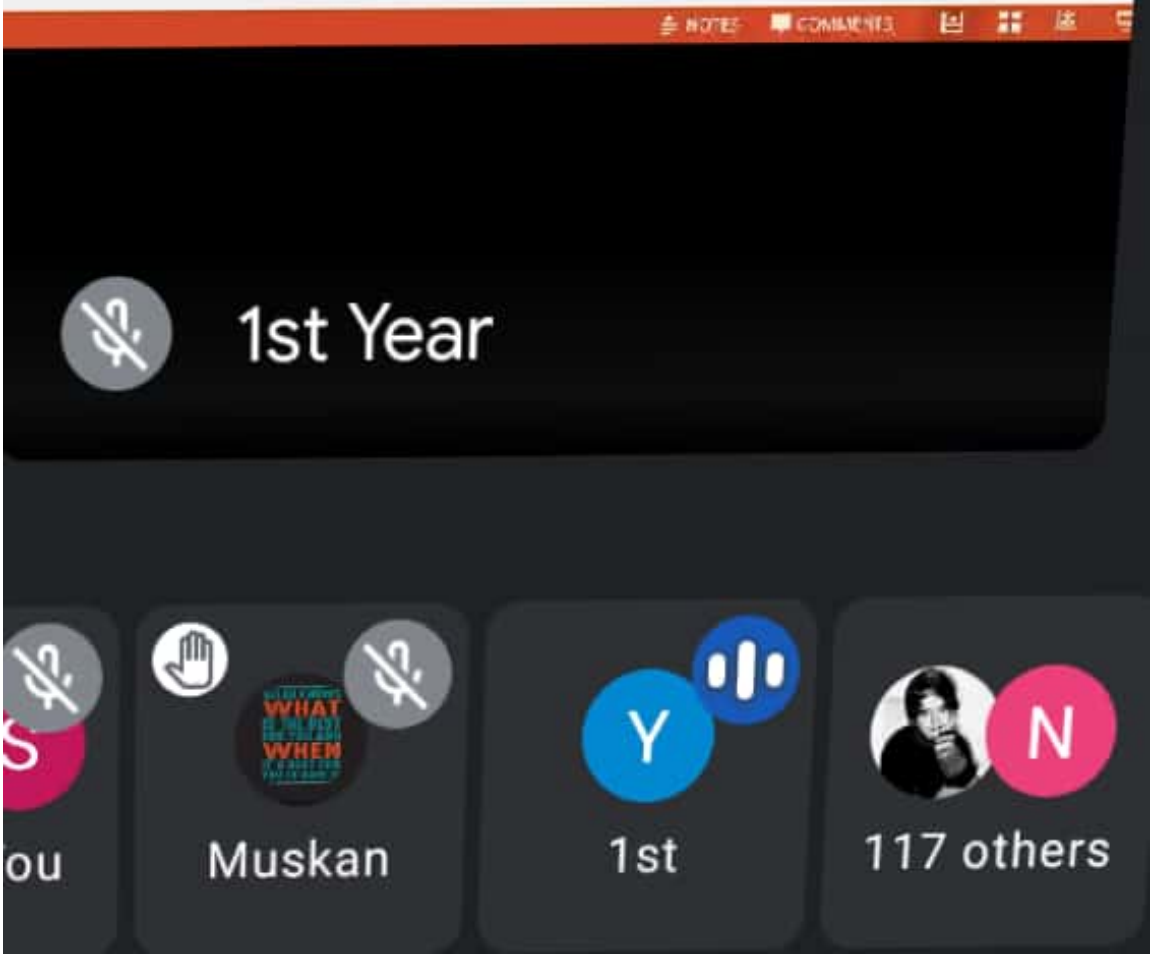


Figure 2-15 Immunobiology, 6/e. © Garland Science 2005



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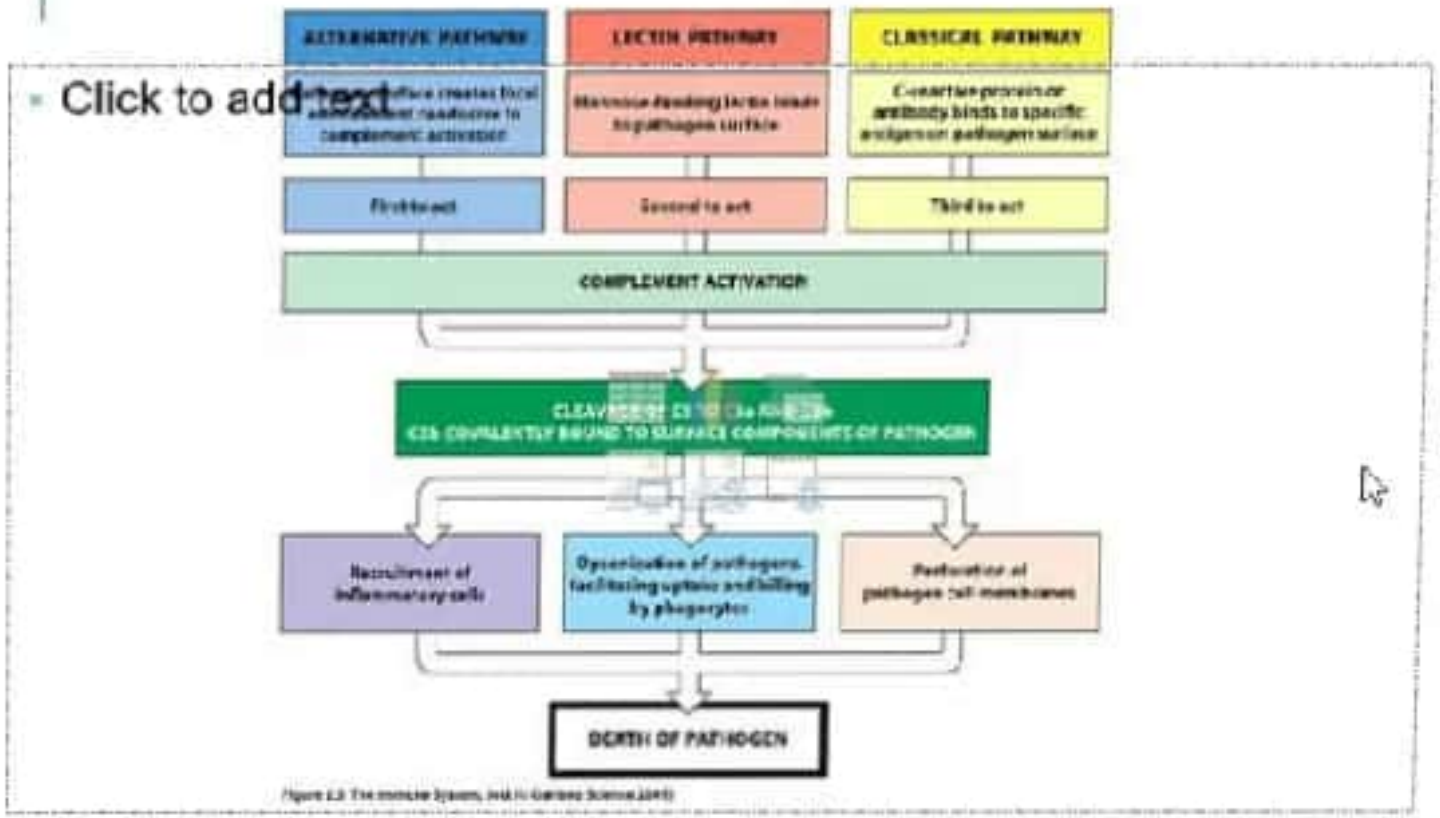
Overview

The Complement System

- Click to add text



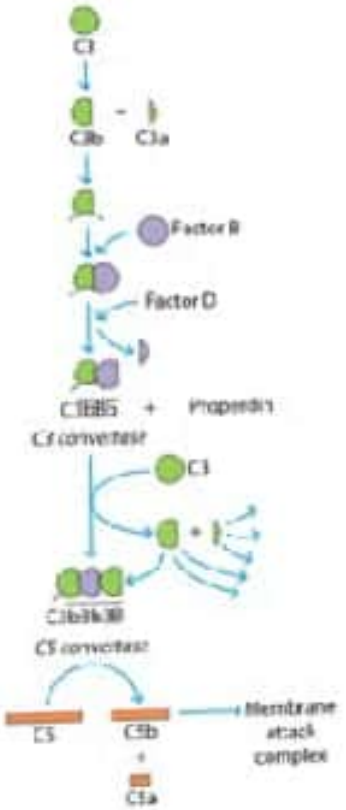
The Alternative Pathway

- The alternative pathway is part of the non-specific defense because it does not need antibodies to initiate the pathway.

- The alternative pathway is slower than the Classical pathway

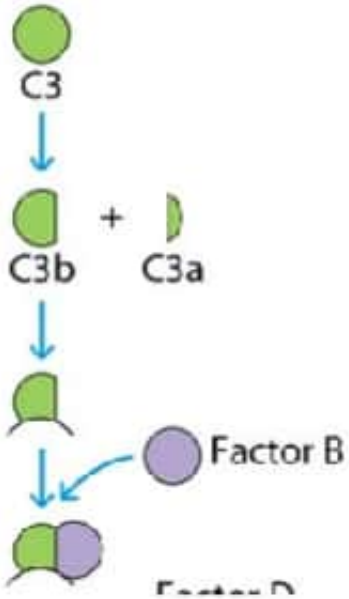
Initiation of The Alternative pathway

- C3 contains an unstable thioester bond.
- This unstable bond makes C3 subject to slow spontaneous hydrolysis to C3b and C3a
- The C3b is able to bind to foreign surface antigens.
- Mammalian cells contain sialic acid which inactivates C3b



Factor B

- C3b on the surface of a foreign cells binds to another plasma protein called factor B



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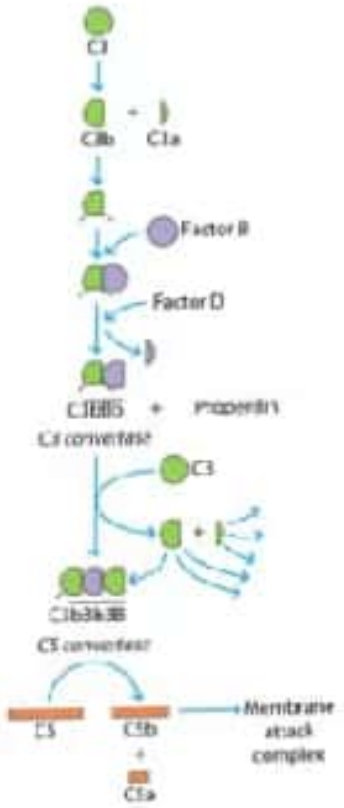
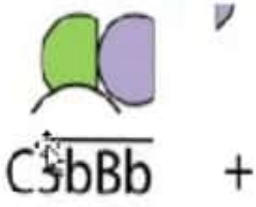
Factor D

- The binding of C3b to factor B allows a protein enzyme called Factor D to cleave Factor B to Ba and Bb.
- Factor Bb remains bound to C3b while Ba and Factor D disperse away.

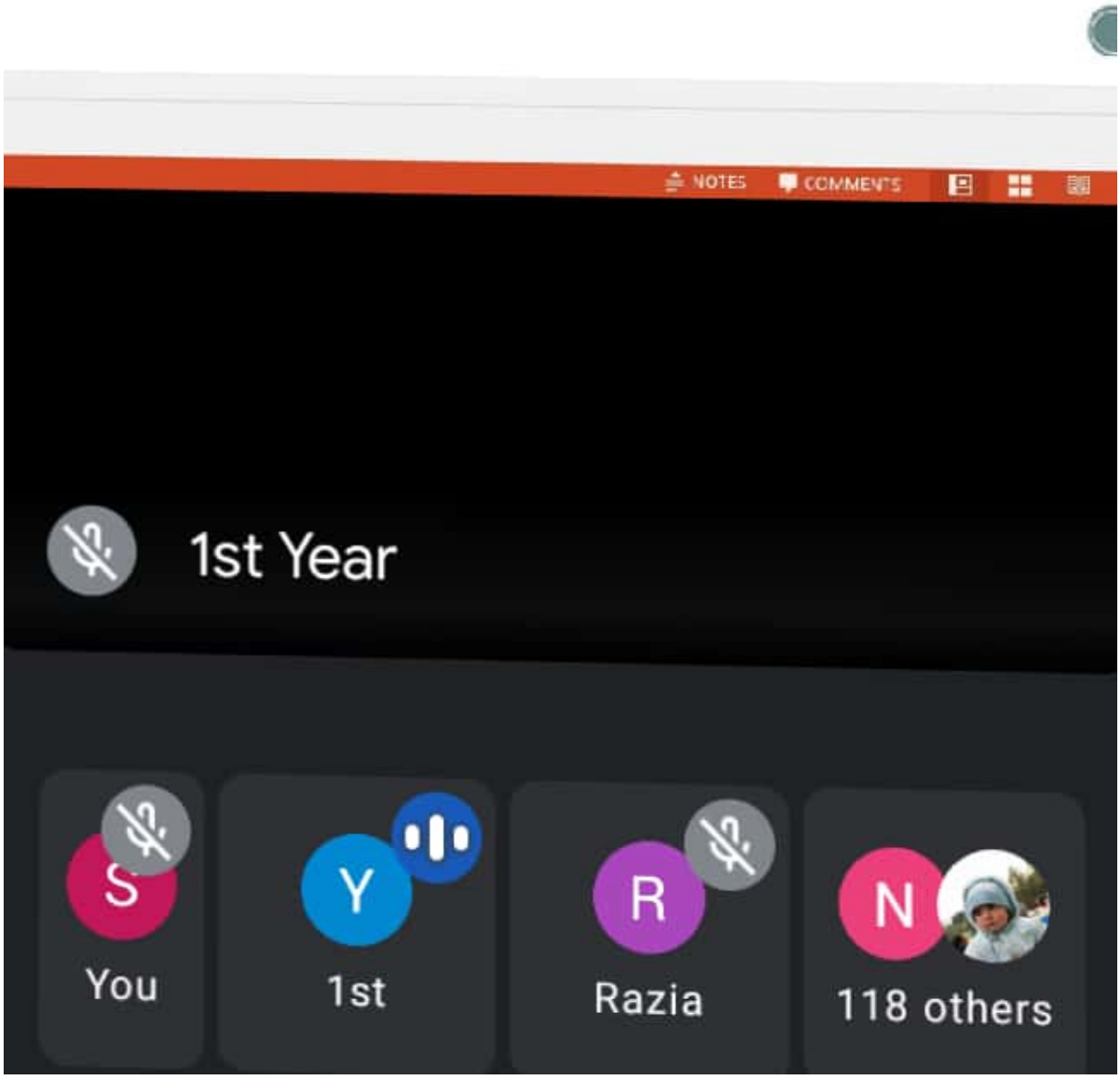


The C3 activation complex



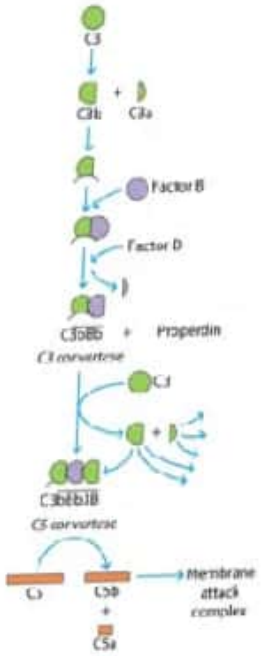
C3bBb + Properdin

- Properdin, also called factor P, binds to the C3bBb complex to stabilize it.
- C3bBbP make up the C3 activation complex for the alternative pathway



The C3 activation Complex

- The C3 activation complex causes the production of more C3b.
- This allows the initial steps of this pathway to be repeated and amplified
- $2X10^6$ molecules can be generated in 5 minutes



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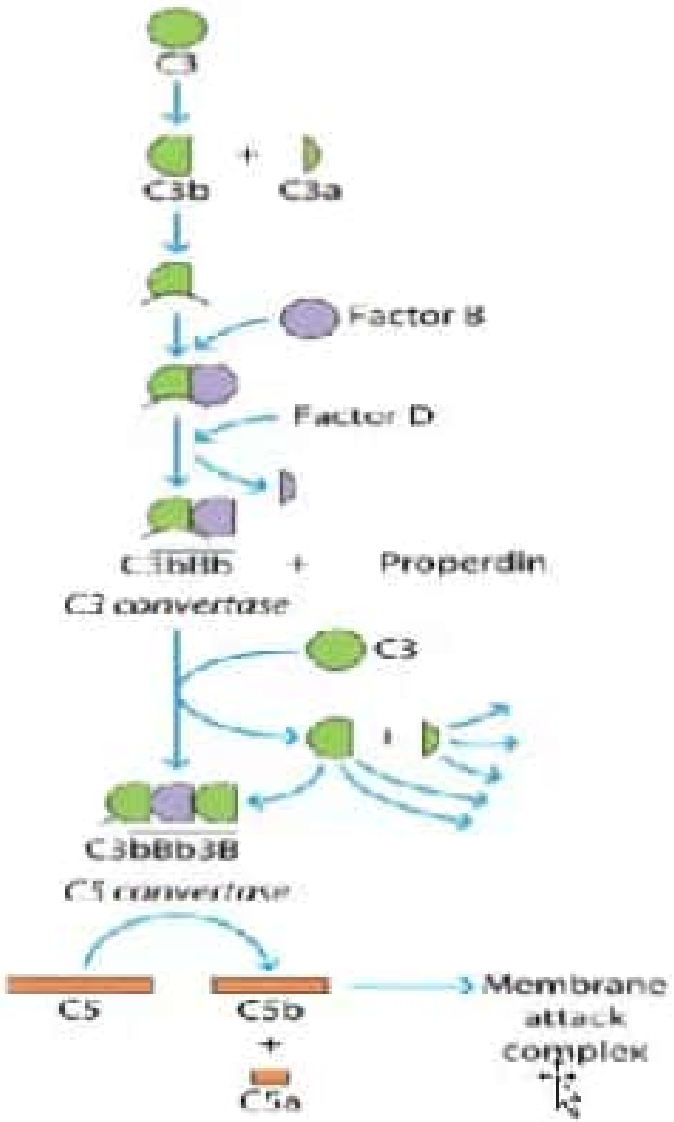
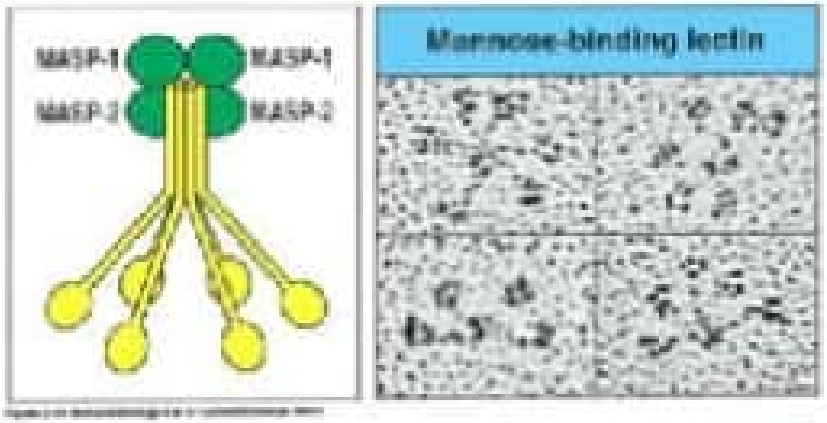
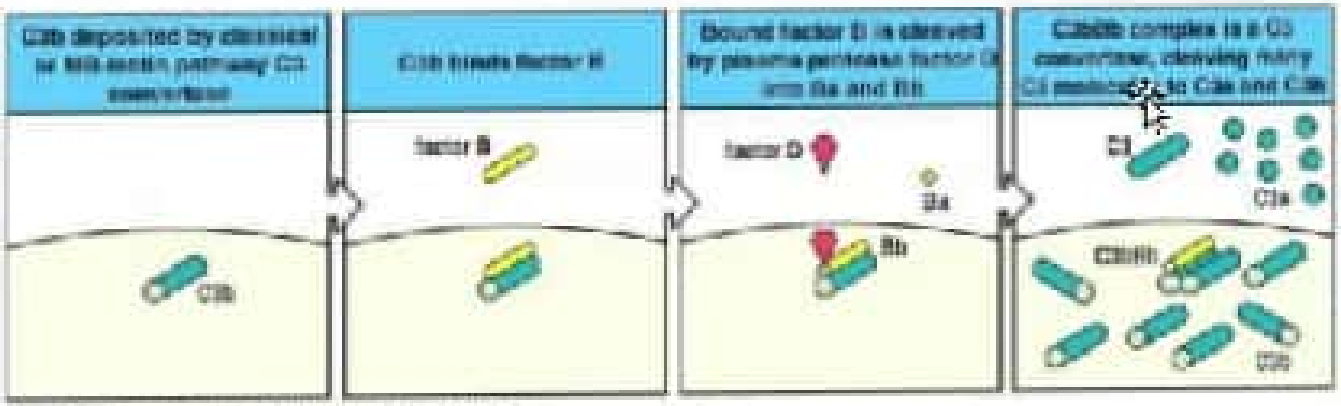


The Alternative complement pathway

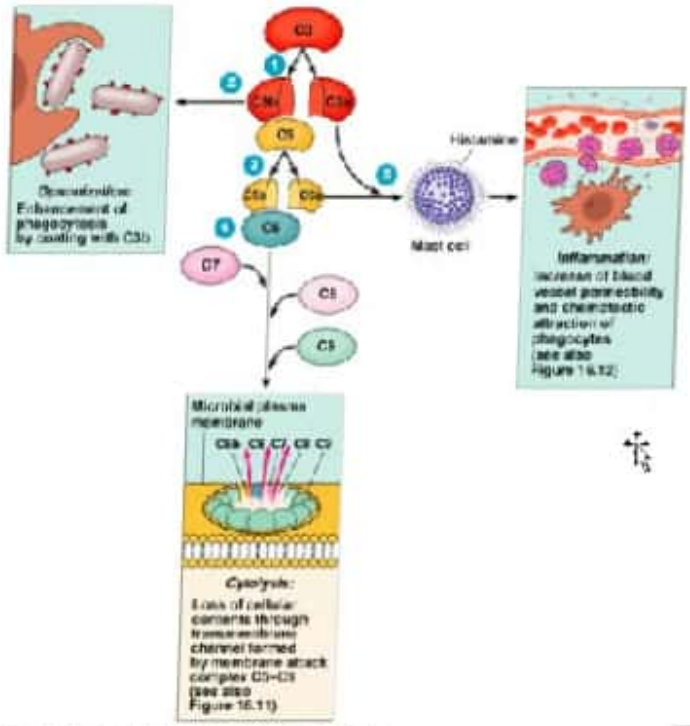
Mannose-Binding Lectin Pathway

Mannose on bacterial cells stimulates MB-lectin to deposit **C3b** on pathogen which forms a **C3 Covertase.**





Overview



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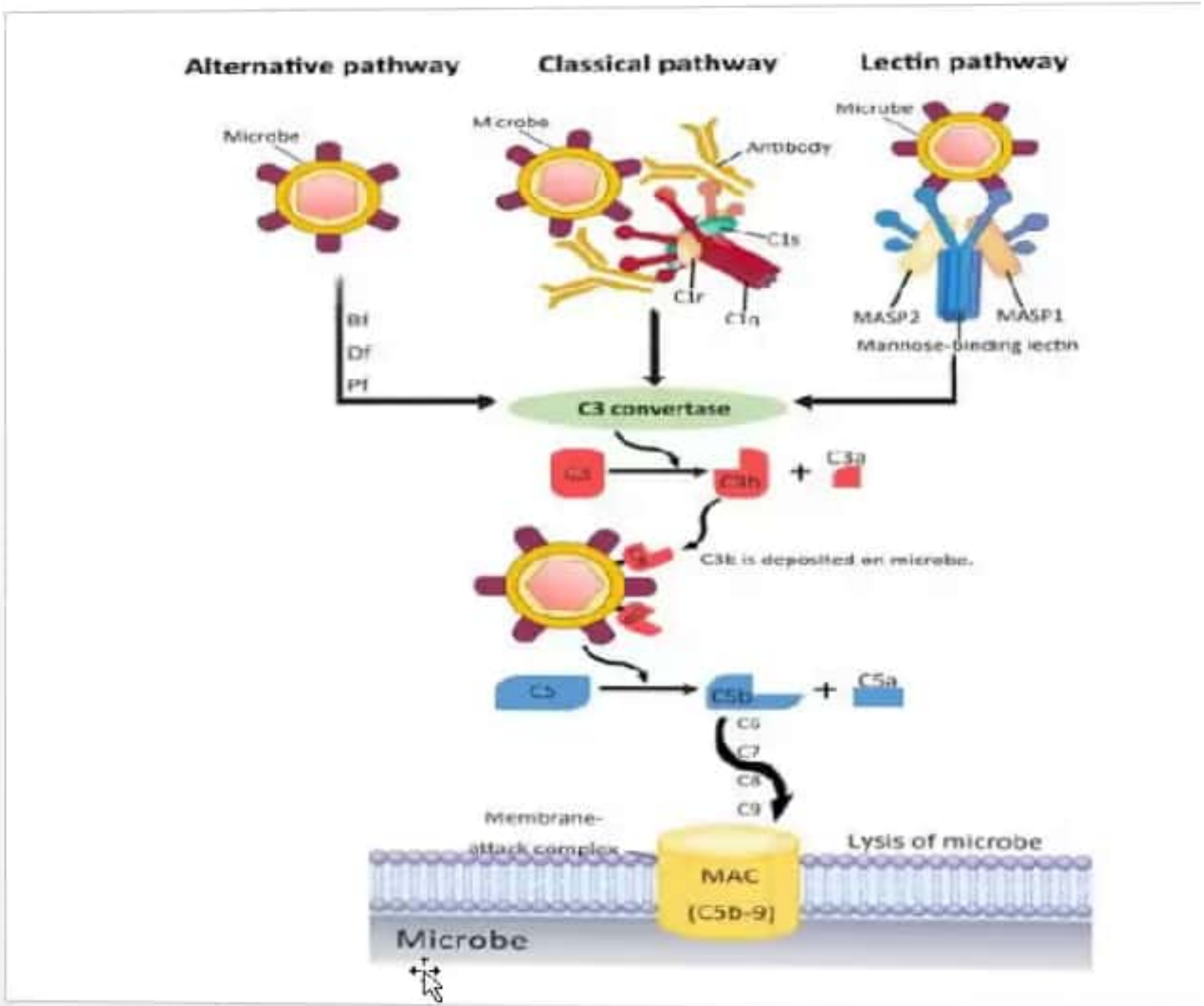
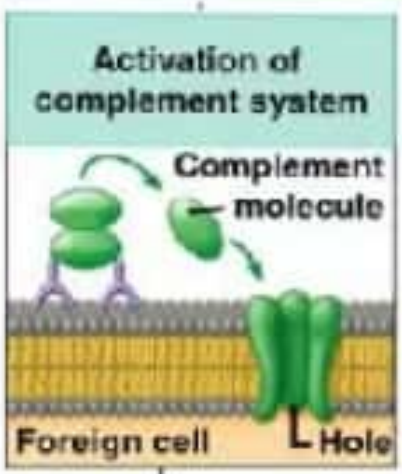
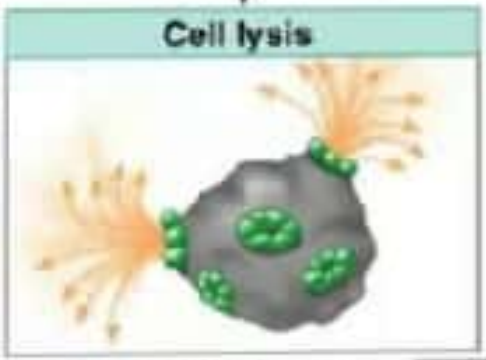


Consequences of Complement Activation



Leads to



- The three complement pathways converge at the membrane-attack complex (MAC).